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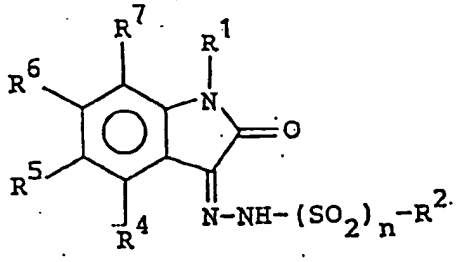
(54) **Hydrazone derivatives, their preparation and use.**

(57) A method of treatment with compounds having the formula



wherein
n is 0 or 1;
R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7}-cycloalkyl, benzyl, phenyl which may be substituted,
acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CONR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)$-NH_2;
R^2 is pyridyl or phenyl, both of which may b substituted one or more times preferably in the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;
R^4, R^5, R^6, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; or R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl, and R^4 and R^5 have the meanings set forth above;
or R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl, and R^6 and R^7 have the meanings set forth above.

Certain of the compounds are novel.

The compounds and pharmaceutical compositions containing the compounds are useful in the treatment of central nervous system disorders and especially conditions sensitive to excitatory amino acids.

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The present invention relates to a method of treatment with compounds having excitatory amino acid antagonizing properties, pharmaceutical compositions comprising such compounds, novel compounds having excitatory amino acid antagonizing properties and to the preparation of such compounds.

Object of the Invention

It is an object of the present invention to provide novel isatine hydrazone compounds which are useful in the treatment of diseases in mammals, including a human, and especially in the treatment of diseases which can be treated by antagonizing an excitatory amino acid of such mammal.

Another object of the present invention is to provide a method of treating disorders in mammals, including a human, responsive to the blockade of glutamic and aspartic acid receptors which comprises administering to a mammal in need thereof a compound of the invention.

A third object of the present invention is to provide novel pharmaceutical compositions for the treatment of disorders in mammals, including a human, responsive to the blockade of glutamic and aspartic acid receptors.

Background of the Invention

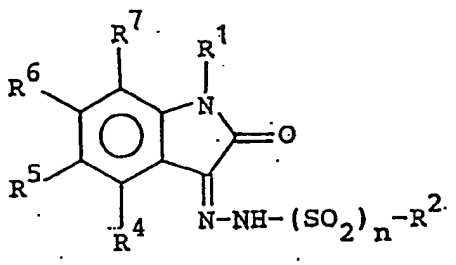
Excessive excitation by neurotransmitters can cause the degeneration and death of neurons. It is believed that this degeneration is in part mediated by the excitotoxic actions of the excitatory amino acids (EAA) glutamate and aspartate at the N-methyl-D-aspartate (NMDA), the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, and the kainate receptor. This excitotoxic action is responsible for the loss os neurons in cerebrovascular disorders such as cerebral ischemia or cerebral infarction resulting from a range of conditions, such as thromboembolic or haemorrhagic stroke, cerebral vasospasm, hypoglycaemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as from drowning, pulmonary surgery and cerebral trauma as well as lathyrism, Alzheimer's, and Huntington's diseases.

The compounds of the present invention may also be useful in the treatment of schizophrenia, parkinsonism, epilepsy, anxiety, pain and drug addiction.

Summary of the Invention

The invention then, inter alia, comprises the following, alon or in combination:

The use of an indole-2,3-dione-3-hydrozone compound having the formula



wherein

n is 0 or 1;

R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7}-cycloalkyl, benzyl, phenyl which may be substituted,

acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CONR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)NH_2$;

R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably in the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, or $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;

R^4, R^5, R^6, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; or R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl, and R^4 and R^5 have the meanings set forth above;

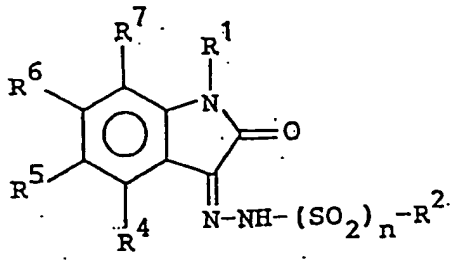
or R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl, and R^6 and R^7 have the meanings set forth above, for the preparation of a medicament useful in the treatment of disorders of a mammal, including a human, responsive to the blockade of glutamic or aspartic receptors,

the use as above wherein at least one of R^4, R^5, R^6 or R^7 is an electron withdrawing substituent such as NO_2, CF_3, CN, $SO_2NR^{11}R^{12}$, or halogen and R^1, R^2, R^4, R^5, R^6, R^7, R^{11}, and R^{12} otherwise have the meanings set forth in claim 1,

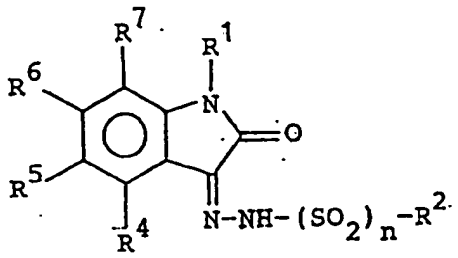
the use as first above wherein R^5 is NO_2, F, CF_3, or CN,

a pharmaceutical composition for use in th treatment of disorders of a mammal, including a human, responsive to the blockade of glutamic or aspartic acid receptors, comprising an effective glutamic or

aspartic acid receptor blocking amount of a compound having the formula

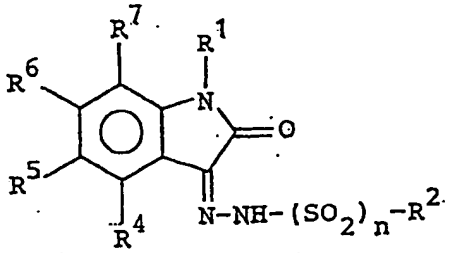


wherein
n is 0 or 1;
R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7}-cycloalkyl, benzyl, phenyl which may be substituted,
acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CONR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)NH_2$;
R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably in the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, or $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;
R^4, R^5 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; and R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl; or R^6, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or
C_{1-6}-alkyl; and R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl;
and R^1, R^4 and R^5 are not all hydrogen when R^2 is unsubstituted phenyl and R^6 and R^7 together form an additional unsubstituted benzo ring,
a compound having the formula

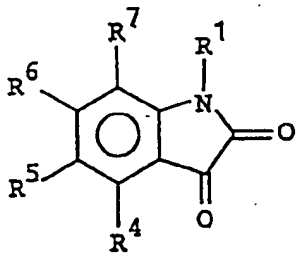


wherein
n is 0 or 1;
R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7}-cycloalkyl, benzyl, phenyl which may be substituted,
acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CONR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)NH_2$;
R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably in the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, or $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;
R^4, R^5 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; and R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl; or R^6, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or
C_{1-6}-alkyl; and R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl;
and R^1, R^4 and R^5 are not all hydrogen when R^2 is unsubstituted phenyl and R^6 and R^7 together form an additional unsubstituted benzo ring,
a compound as above wherein the additional ring formed by R^6 and R^7 or R^4 and R^5 is substituted with halogen, NO_2, CF_3, CN or $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl,
a compound as abov , which is 8-nitro-1H-4,5,6,7-tetrahydrobenz[e]indole-2,3-dione-3-(2-nitrophenylhydrazone,
a compound as abov , which is 5-nitro-1H-6,7,8,9-

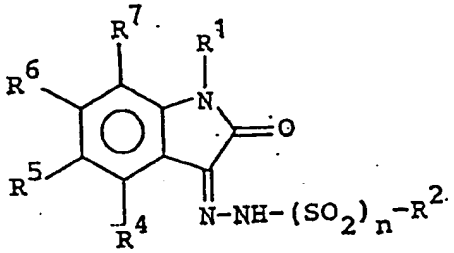
tetrahydrobenz[g]indole-2,3-dione-3-phenylsulphonylhydrazone,
a compound as above, which is 5-nitro-1H-6,7,8,9-tetrahydrobenz[g]indole-2,3-dione-3-(2-pyridylhydrazone),
a method of preparing a compound having the formula



wherein
n is 0 or 1;
R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7}-cycloalkyl, benzyl, phenyl which may be substituted,
acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CONR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)NH_2$;
R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably in the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, or $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;
R^4, R^5 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; and R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently ar hydrogen, benzyl, or C_{1-6}-alkyl; or R^6, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or
C_{1-6}-alkyl; and R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl;
and R^1, R^4 and R^5 are not all hydrogen when R^2 is unsubstituted phenyl and R^6 and R^7 together form an additional unsubstituted benzo ring,
comprising the step of reacting a compound of the formula



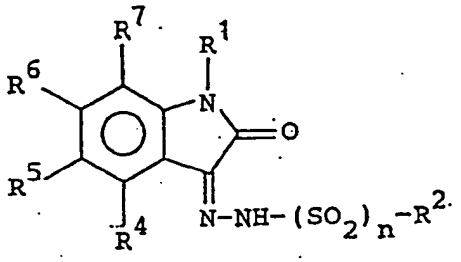
wherein R^1, R^4, R^5, R^6 and R^7 have the meanings set forth above, with a compound having the formula $H_2N\text{-}MH\text{-}(SO_2)_nR^2$, wherein R^2 and n have the meanings set forth above,
a method of preparing a pharmaceutical preparation comprising mixing as active ingredient an effective amount of a compound having the formula



wherein
n is 0 or 1;
R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7}-cycloalkyl, benzyl, phenyl which may be substituted,
acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CONR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)NH_2$;
R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably in the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, or $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;
R^4, R^5, R^6, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; or R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl, and R^4 and R^5 hav the meanings set forth abov ;

or R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl, and R^6 and R^7 have the meanings set forth above, with at least one pharmaceutical acceptable carrier and/or diluent,

a method of treating disorders of a mammal, including a human, responsive to the blockade of glutamic or aspartic acid receptors, which comprises administering to a patient in need thereof an effective excitatory amino acid blocking amount of an indole-2,3-dione-3-hydrazone compound having the formula



wherein

n is 0 or 1;

R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7}-cycloalkyl, benzyl, phenyl which may be substituted,

acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CON^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)NH_2$;

R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably in the ortho and para positions with halogen, CF_3, MO_2, CN, phenyl, or $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;

R^4, R^5, R^6, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; or R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, MO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl, and R^4 and R^5 hav the meanings set forth above;

or R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring which may b aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl, and R^6 and R^7 have th meanings set forth above,

the method as above wherein at least one of R^4, R^5, R^6 or R^7 is an electron withdrawing substituent such as NO_2, CF_3, CN, $SO_2NR^{11}R^{12}$, or halogen and R^1, R^2, R^4, R^5, R^6, R^7, R^{11}, and R^{12} otherwis have the meanings set forth above,

the method as above wherein R^5 is NO_2, F, CF_3, or CN,

the method as above, wherein the compound is administered in the form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent.

Biological Activity

The compounds of the invention exhibit valuable biological properties because of their strong excitatory amino acid (EAA) (glycine, glutamate, quisqualate, ATPA (α-amino-3-hydroxy-5-t-butylisoxazole-4-propionic acid), AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid), kainate, NMDA (M-methyl-D-aspartate)) antagonizing properties.

Compounds of the invention show potent affinity for the glutamate subreceptor binding sites for kainate, NMDA, quisqualate and glycine. Thes properties make the compounds useful in the treatment of human malfunctions related to the excitatory amino acids (EAA).

Compounds of the invention exhibit binding at the ^{3}H-kainate, NMDA, ^{3}H-AMPA and/or ^{3}H-glycine binding sites with IC_{50} in the range of 1-100 μM. Examples of such compounds are for example

Z,E-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-phenylhydrazone,

Z,E-1H-5-nitro-benz[g]indole-2,3-dione-3-phenylhydrazone,

E-5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-(2-nitrophenylhydrazone),

Z-1H-indole-2,3-dione-3-(2,4-dinitrophenylhydrazone),

Z-5,7-dinitro-1H-indole-2,3-dione-3-phenylhydrazone,

5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-phenylsulphonehydrazide,

5,9-dinitro-1H-benz[g]indole-2,3-dione-3-phenylsulphonehydrazide.

The quisqualate binding assay was performed as described by T. Honoré et al., Meuroscienc Letters 54, 27-32 (1985).

The kainate binding assay was performed as described by T. Honoré et al., Neuroscience Letters 65, 47-52 (1986).

The glycine binding assay was performed as described by W. Frost White et al., Journal of Meurochemistry 53(2), 503-512 (1989).

Pharmaceutical Compositions

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of active ingredients or, more broadly, 0.1 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

Method of Treating

Th compounds of this invention are extremely useful in the treatment of central nervous system disorders related to their biological activity. The compounds of this invention may accordingly be administered to a subject, including a human, in need of treatment, alleviation, or elimination of an indication associated with the biological activity of the compounds. This includes especially excitatory amino acid dependent psychosis, excitatory amino acid dependent anoxia, excitatory amino acid dependent ischemia, excitatory amino acid dependent convulsions and excitatory amino acid dependent migraine. Suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or v terinarian in charge.

Chemical Examples

Some compounds of the invention are old, and others are novel chemical entities. In any-way the compounds of the invention may be prepared according to chemical methods which are well known for a person skilled in the art.

Example 1

a) 1-phenyl-1H-indole-2,3-dione.

To a stirred solution of diphenylamine (3.2 g, 20 mmol) and 4-dimethylaminopyridine (10 mg) in chloroform (50 ml) was dropwise added oxalylchloride (3 ml). The resulting mixture was refluxed for 5 hours, whereafter it was cooled to room temperature and evaporated in vacuo.

The residue (oil) was redissolved in methylene chloride (50 ml) and dry $AlCl_3$ (3 g) was added. Stirring at room temperature was continued for 30 hours, whereafter ethanol (10 ml) followed by water (100 ml) were added. The organic phase was washed with saturated Na_2CO_3, dried over Na_2SO_4 and evaporated. The crystalline residue was stirred in ether (40 ml) and the product was filtered off. Yield: 2.65 g orange crystals, M.p. 139-141 °C, litt. 138 °C.

b) The following 1H-indole-2,3-diones were prepared according to known literature procedures.

[1)]Organic Synthesis Col Vol. I p. 327.

[2)]Martinet, J.: Compt. Rend. 166, 851, 1918.

4,6-ditrifluoromethyl-1H-indole-2,3-dione[1)], M.p. 162-165 °C.

1H-benz[g]indole-2,3-dione[2)], M.p. 242-245 °C.

7-trifluoromethyl-1H-indole-2,3-dione[1)], M.p. 181-183 °C.

1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione, M.p. 224-226 °C.

6-methoxy-1H-indole-2,3-dione, M.p. >310 °C.

7-trifluoromethyl-1H-indole-2,3-dione, M.p. 180-184 °C.

c) 1-methyl-5-nitro-7-trifluoromethyl-1H-indole-2,3-dione.

To a stirred 10 °C warm solution of KNO_3 - (0.5 g) in 10 ml of conc. H_2SO_4 was dropwise added a solution of 1-methyl-7-trifluoromethyl-1H-indole-2,3-dione in 10 ml of conc. H_2SO_4. The addition was completed after 10 min, whereafter stirring was continued for 15 min at room temperature. The reaction mixture was poured on ice whereby the title compound precipitated as yellow crystals. The crystals were collected by filtration and washed with water. M.p. 168-169 °C.

In a similar manner to c), the following nitro compounds were prepared:

5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione, M.p. 232-236 °C.

5-nitro-1-methyl-1H-benz[g]indole-2,3-dione, M.p. 255-258 °C.

d) 5,7-dinitro-1-methyl-1H-indole-2,3-dione.

To a stirred solution of 5,7-dinitro-1H-indole-2,3-dione (1.2 g) in dry dimethylformamide (20 ml) was added sodium hydride (0.24 g 55% in mineral oil). After the hydrogen evolution had ceased methyl iodide (0.37 ml) was added. Stir-

ring at room temperature was continued for 2 hours, whereafter the crude product was precipitated as an oil by addition of water (100 ml) to the reaction mixture. The oil crystallized upon treatment with ether/pentane, M.p. 154-157 °C.

In a similar manner to d), the following 1-alkyl- or 1-benzyl-1H-indole-2,3-diones were prepared.

5,7-dinitro-1-ethyl-1H-indole-2,3-dione, M.p. 135-140 °C.

5-bromo-1-methyl-1H-indole-2,3-dione, M.p. 157-160 °C.

1H-1-methyl-6,7,8,9-tetrahydro-benz[g]-indole-2,3-dione, M.p. 157-160 °C.

5,7-dibromo-1-methyl-1H-indole-2,3-dione, M.p. 170-173 °C.

5,6-dichloro-1-methyl-1H-indole-2,3-dione, M.p. 180-184 °C.

4,5-dichloro-1-methyl-1H-indole-2,3-dione, M.p. 237-239 °C.

1-methyl-5-nitro-1H-indole-2,3-dione, M.p. 196-199 °C.

1-benzyl-5,7-dinitro-1H-indole-2,3-dione, M.p. 127-131 °C.

4,6-ditrifluoromethyl-1-methyl-1H-indole, M.p. 93-94 °C.

1-methyl-7-trifluoromethyl-1H-indole-2,3-dione, M.p. 120-122 °C.

6-methoxy-1-methyl-1H-indole-2,3-dione, M.p. 175-178 °C.

5,7-dinitro-1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione, (oil).

1-methyl-1H-benz[g]indole-2,3-dione, M.p. 122-126 °C.

1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione, M.p. 115-119 °C.

5,7-dibromo-1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione, M.p. 97-102 °C.

1-methyl-1H-6,7,8,9-tetrahydrobenz[g]indole-2,3-dione, M.p. 160-165 °C.

e) 5-dimethylsulfamoyl-1H-indole-2,3-dione.

10 g (68 mmol) isatin was added to 30 ml of chlorosulfonic acid at 30 °C for 30 minutes and was thereafter poured dropwise onto ice. A crude material was obtained (14.5 g). 7 g of this crude material was added to dimethylamine in water and ethyl acetate. This reaction mixture was stirred at RT for 1 hour and the organic phase was evaporated to yield and oil which was stirred with 1N hydrochloric acid in hot ethyl acetate. This mixture was extracted with ethyl acetat , which was evaporated in vacuo. The residue was recrystallized from ethanol. Yield of th title compound 550 mg, M.p. 265-266 °C.

In a similar manner th following compounds wer prepared:

5-sulfamoyl-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione, M.p. >350 °C.

Example 2

E-5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-(2-nitrophenylhydrazone)

0.5 g (2 mmol) of 5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione, 0.34 g (2.2 mmol) 2-nitrophenylhydrazin and 2 drops of 1N HCl were dissolved in 15 ml of methanol and the mixture was stirred at room temperature for 30 minutes. The precipitate was isolated by filtration. The crude reaction product consisted of a mixture of the two isomers (Z and E forms) of the title compound. The title compound was obtained by washing the crude reaction product with tetrahydrofuran (THF) due to different solubility of the E and Z isomer in THF. Yield 350 mg of the title compound. M.p. >350 °C.

In similar way the following compounds were prepared from the appropriate isatine and hydrazine or sulphonehydrazide compounds. The Z and E isomers were obtained by utilizing their different solubility in THF. Furthermore an E isomer may be transformed into a Z isomer by heating in THF.

Z,E-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-phenylhydrazone, M.p. 288-290 °C.

E-1H-5,7-dinitro-1-methyl-indole-2,3-dione-3-(2-nitrophenylhydrazone), M.p. 320-321 °C.

Z-1-phenyl-1H-indole-2,3-dione-3-(2-nitrophenylhydrazone), M.p. 191-194 °C.

E-1-phenyl-1H-indole-2,3-dione-3-(2-nitrophenylhydrazone), M.p. 206-210 °C.

Z/E-5-nitro-1H-benz[g]indole-2,3-dione-3-phenylhydrazone, M.p. 294-295 °C.

Z-5-nitro-1H-indole-2,3-dione-3-phenylhydrazone, M.p. 279-281 °C.

Z-5,7-dinitro-1H-indole-2,3-dione-3-phenylhydrazone, M.p. 301-302 °C.

Z-1H-indole-2,3-dione-3-(2,4-dinitrophenylhydrazone), M.p. 344-348 °C.

Z-1H-indole-2,3-dione-3-phenylhydrazone, M.p. 203-205 °C.

E-1H-indole-2,3-dione-3-(2-nitrophenylhydrazone), M.p. 288-291 °C.

5,9-dinitro-1H-benz[g]indole-2,3-dione-3-phenylsulphonylhydrazone, M.p. 144-146 °C.

5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-phenylsulphonylhydrazone, M.p. 173-175 °C.

5-nitro-1H-benz[g]indole-2,3-dione-3-phenylsulphonylhydrazone, M.p. 195-198 °C.

5,7-dinitro-1H-indole-2,3-dione-3-phenylsulphonylhydrazone, M.p. 200-202 °C.

Example 3

The following compounds as E, Z or E/Z isomers are prepared according to the same procedure as given in example 2 by combinations of different isatine derivatives and hydrazines.

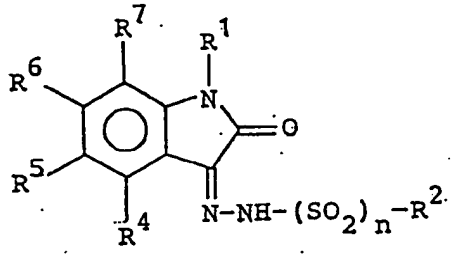
5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-(2-pyridylhydrazone),
5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-(4-fluorophenylhydrazone),
1H-5,7-dinitro-indole-2,3-dione-3-(4-sulfamoylphenylhydrazone),
7-CF_3-1H-indole-2,3-dione-3-(2-nitrophenylhydrazone),
4,6-ditrifluoromethyl-1H-indole-2,3-dione-3-(2-nitrophenylhydrazone),
1-methyl-5-nitro-7-trifluoromethyl-1H-2,3-dione-3-(2-nitrophenylhydrazone),
5,6-dicloro-1-methyl-1H-indole-2,3-dione-3-(2-pyridylhydrazone),
5-dimethylsulfamoyl-1H-indole-2,3-dione-3-(2-nitrophenylhydrazone),
7-sulfamoyl-8-nitro-benz[e]indole-2,3-dione-3-(2-nitrophenylhydrazone),
8-nitro-4,5,6,7-tetrahydro-benz[e]indole-2,3-dione-3-(2-nitrophenylhydrazone),
7-sulfamoyl-8-nitro-benz[e]indole-2,3-dione-3-phenylsulphonylhydrazone,
8-sulfamoyl-4,5,6,7-tetrahydro-benz[e]indole-2,3-dione-3-phenylsulphonylhydrazone.

It is thus seen that the present invention provides a new and convenient process for the production of indole-2,3-dione-3-hydrazone compounds, certain novel indole-2,3-dione-3-hydrazone compounds which are useful as excitatory amino acid antagonists, pharmaceutical-compositions useful as excitatory amino acid antagonists comprising certain indole-2,3-dione-3-hydrazone compounds, and a method of antagonizing the biological effects of excitatory amino acids in a subject in need thereof comprising the step of administering certain indole2,3-dione-3-hydrazone compounds or a pharmaceutical composition comprising the same together with a pharmaceuticallyacceptable diluent or carrier, all having the foregoing characteristics and advantages.

It is to be understood that the invention is not to be limited to the exact details of operation, or to th exact methods, procedures, or embodiments shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the full scope of the appended claims.

Claims

1. The use of an indole-2,3-dione-3-hydrozone compound having th formula

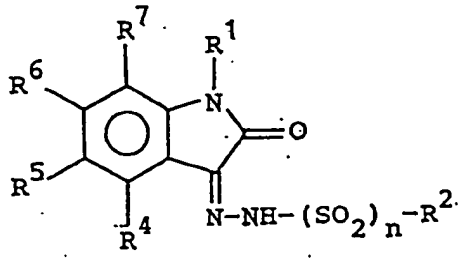


wherein
n is 0 or 1;
R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7}-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CONR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)NH_2$;
R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably in the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, or $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;
R^4, R^5, R^6, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; or R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl, and R^4 and R^5 have the meanings set forth above;
or R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or
C_{1-6}-alkyl, and R^6 and R^7 have the meanings set forth above, for the preparation of a medicament useful in the treatment of disorders of a mammal, including a human, responsive to the blockade of glutamic or aspartic receptors.

2. The use according to claim 1 wherein at least one of R^4, R^5, R^6 or R^7 is an electron withdrawing substituent such as NO_2, CF_3, CN, $SO_2NR^{11}R^{12}$, or halogen and R^1, R^2, R^4, R^5, R^6, R^7, R^{11}, and R^{12} otherwise have th meanings set forth in claim 1.

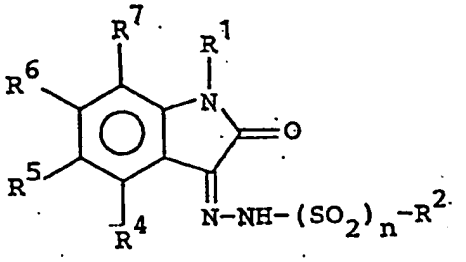
3. Th us according to claim 1 wherein R^5 is NO_2, F, CF_3, or CN.

4. A pharmaceutical composition for use in the treatment of disorders of a mammal, including a human, responsive to the blockade of glutamic or aspartic acid receptors, comprising an effective glutamic or aspartic acid receptor blocking amount of a compound having the formula



wherein
n is 0 or 1;
R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7}-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CONR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)NH_2$;
R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably in the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, or $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;
R^4, R^5 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; and R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl; or R^5, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} indep ndently are hydrogen, benzyl, or
C_{1-6}-alkyl; and R^4 and R^5 togeth r form an additional 4 to 8 m mbered carbocyclic ring which may b aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl;
and R^1, R^4 and R^5 are not all hydrogen when R^2 is unsubstituted phenyl and R^6 and R^7 together form an additional unsubstituted benzo ring.

5. A compound having the formula



wherein
n is 0 or 1;
R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7}-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CONR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)NH_2$;
R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably in the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, or $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;
R^4, R^5 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; and R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl; or R^5, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or
C_{1-6}-alkyl; and R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring which may b aromatic or partial saturated and which may b substituted with halogen, NO_2,

CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently ar hydrogen, benzyl, or C_{1-6}-alkyl;
and R^1, R^4 and R^5 are not all hydrogen when R^2 is unsubstituted phenyl and R^6 and R^7 together form an additional unsubstituted benzo ring.

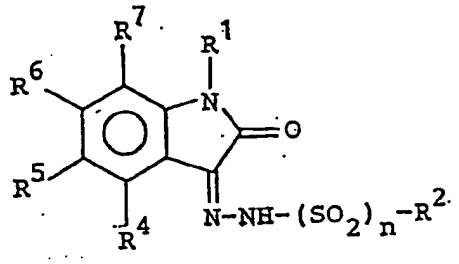
6. A compound according to claim 5 wherein the additional ring formed by R^6 and R^7 or R^4 and R^5 is substituted with halogen, NO_2, CF_3, CN or $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl.

7. A compound of Claim 5, which is 8-nitro-1H-4,5,6,7-tetrahydro-benz[e]indole-2,3-dione-3-(2-nitrophenyl hydrazone.

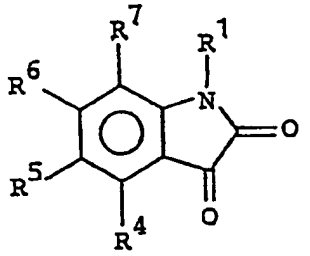
8. A compound of Claim 5, which is 5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-phenylsulphonylhydrazone.

9. A compound of Claim 5, which is 5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-(2-pyridylhydrazone).

10. A method of preparing a compound having the formula

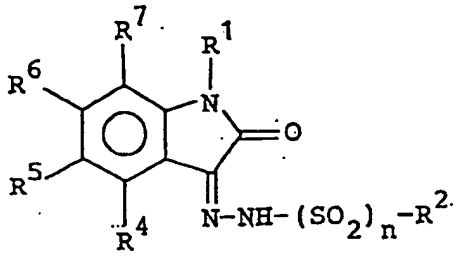


wherein
n is 0 or 1;
R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7} cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CONR^{IV}R^{V}$ wherein R^{IV} and R^{V} independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)NH_2$;
R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably in the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, or $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;
R^4, R^5 independ ntly ar hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; and R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl; or R^6, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or
C_{1-6}-alkyl; and R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl;
and R^1, R^4 and R^5 are not all hydrogen when R^2 is unsubstituted phenyl and R^6 and R^7 together form an additional unsubstituted benzo ring,
comprising the step of reacting a compound of the formula



wherein R^1, R^4, R^5, R^6 and R^7 have the meanings set forth above, with a compound having the formula H_2N-NH-$(SO_2)_nR^2$, wherein R^2 and n have the meanings set forth above.

11. A method of preparing a pharmaceutical preparation comprising mixing as active ingredient an effective amount of a compound having the formula



wherein
n is 0 or 1;
R^1 is hydrogen, C_{1-6}-alkyl which may be branched, C_{3-7}-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C_{1-6}-alkoxy, CH_2CO_2R' wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, $CH_2CONR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen or C_{1-6}-alkyl, or $CH_2C(=NOH)NH_2$;
R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably in the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, or $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6}-alkyl;
R^4, R^5, R^6, R^7 independently are hydrogen, C_{1-6}-alkyl which may be branched, phenyl, halogen, C_{1-6}-alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6}-alkyl; or R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6}-alkyl, and R^4 and R^5 have the meanings set forth above;
or R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are hydrogen, benzyl, or
C_{1-6}-alkyl, and R^6 and R^7 have the meanings set forth above with at least one pharmaceutical acceptable carrier and/or diluent.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 3104

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
P,Y	EP-A-0 432 648 (NEUROSEARCH A/S) 19 June 1991 *whole document, especially claim 1 and pages 6-7*	1-9	C07D209/40 C07D209/60 C07D401/12 A61K31/40
X	DE-A-2 314 242 (BAYER AG) 26 September 1974 *page 12, formula XI, and definitions of R2-R5 on page 4, and of R11 on page 11*	5,6	A61K31/44
A	CHEMICAL ABSTRACTS, vol. 103, no. 3, 22 July 1985, Columbus, Ohio, US; abstract no. 16405S, 'REVERSIBLE INHIBITORS OF MONOAMINE OXIDASE IN THE INDOLINONE SERIES' page 17 ; * abstract *	1-4	
A	CHEMICAL ABSTRACTS, vol. 109, no. 15, 10 October 1988, Columbus, Ohio, US; abstract no. 125673X, 'STUDIES ON HETEROCYCLIC COMPOUNDS; INDOLE-2,3-DIONE DERIVATIVES.' page 372 ; * abstract *	1-4	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
Y	INDIAN DRUGS vol. 22, no. 12, 1985, pages 633 - 639; 'SYNTHESIS AND PHARMACOLOGICAL SCREENING OF 1-(SUBSTITUTED ACYL/ARYLOXY/ARYLSULPHONYL)-2-OXO-3(PHENYLSULPHONYLHYDRAZONO)-5-SUBSTITUTED INDOLES.'	1-9,10	C07D A61K
X	*COMPOUNDS 25-40, TABLE 2*	1-4,11	
Y	INDIAN DRUGS vol. 27, no. 11, 1990, pages 563 - 567; 'SYNTHESIS AND PHARMACOLOGICAL SCREENING OF 1-(SUBSTITUTED-AMINOMETHYL)-2-OXO-3 (PHENYL/P-TOLYL SULPHONYLHYDRAZONO)-5-SUBSTITUTED INDOLES.' *COMPOUNDS 5-8 AND 9-32*	1-9	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	01 JUNE 1992	SCRUTON-EVANS I.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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EUROPEAN SEARCH REPORT

Application Number

EP 92 10 3104

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	JOURNAL OF HETEROCYCLIC CHEMISTRY vol. 21, no. 6, November 1984, pages 1641 - 1645; 'POTENTIAL ANTICONVULSANTS. IX. SOME ISATIN HYDRAZONES AND RELATED COMPOUNDS'	1-9,10	
X		1-4,11	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	01 JUNE 1992	SCRUTON-EVANS I.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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